

# HLA-DQA1\*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease

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Anderson group  
Wellcome Sanger Institute

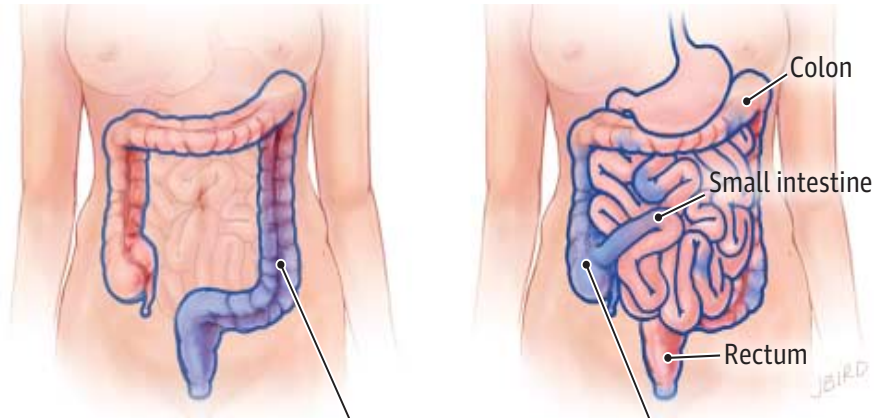
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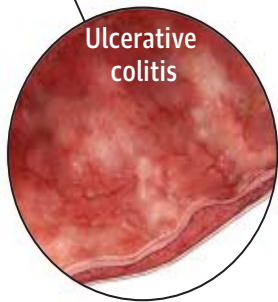
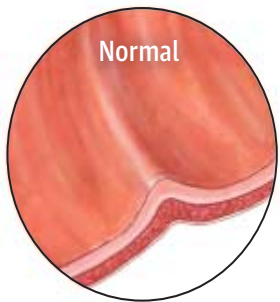
# Inflammatory Bowel Disease (IBD)

Ulcerative Colitis (UC)

Crohn's Disease (CD)

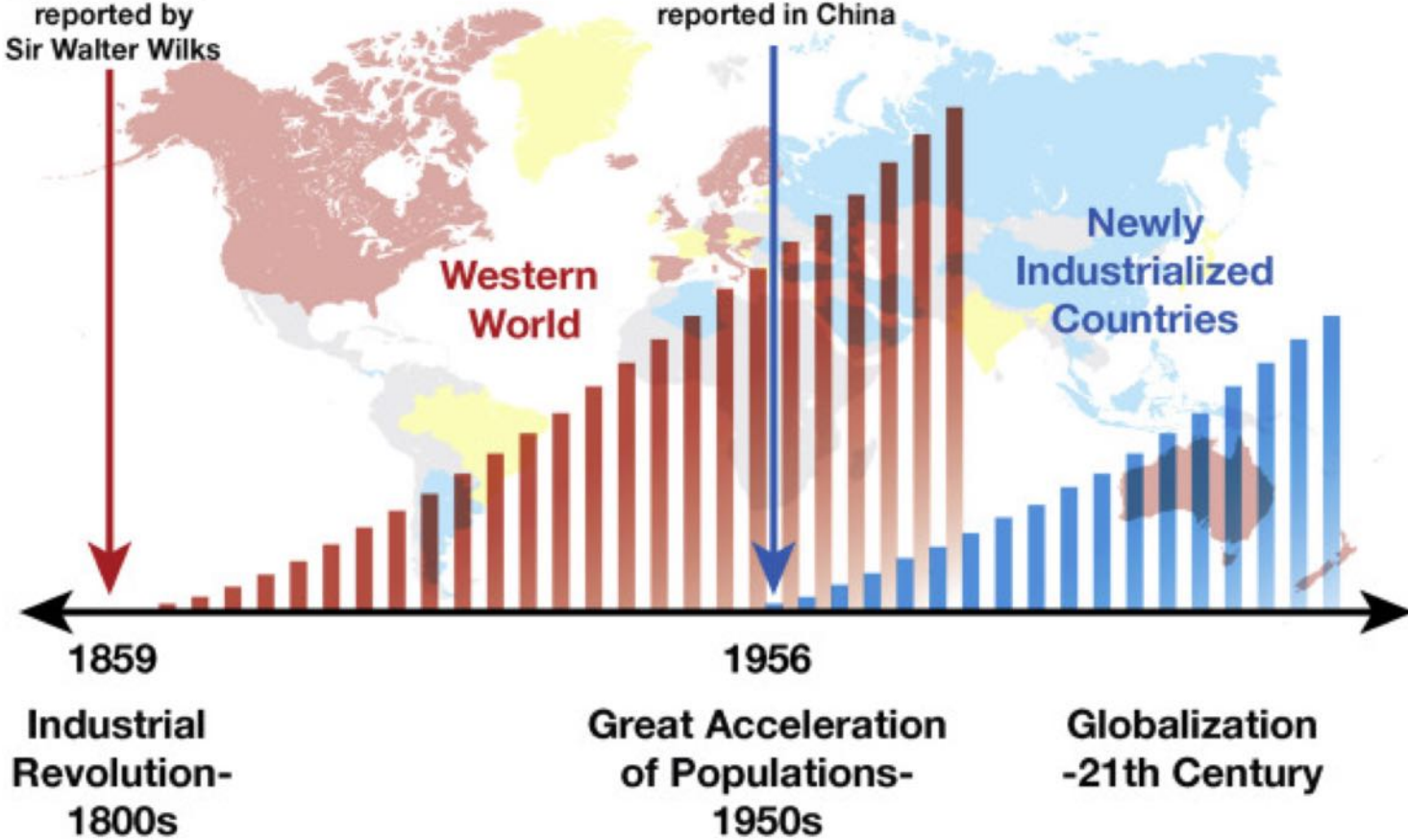


Colon wall

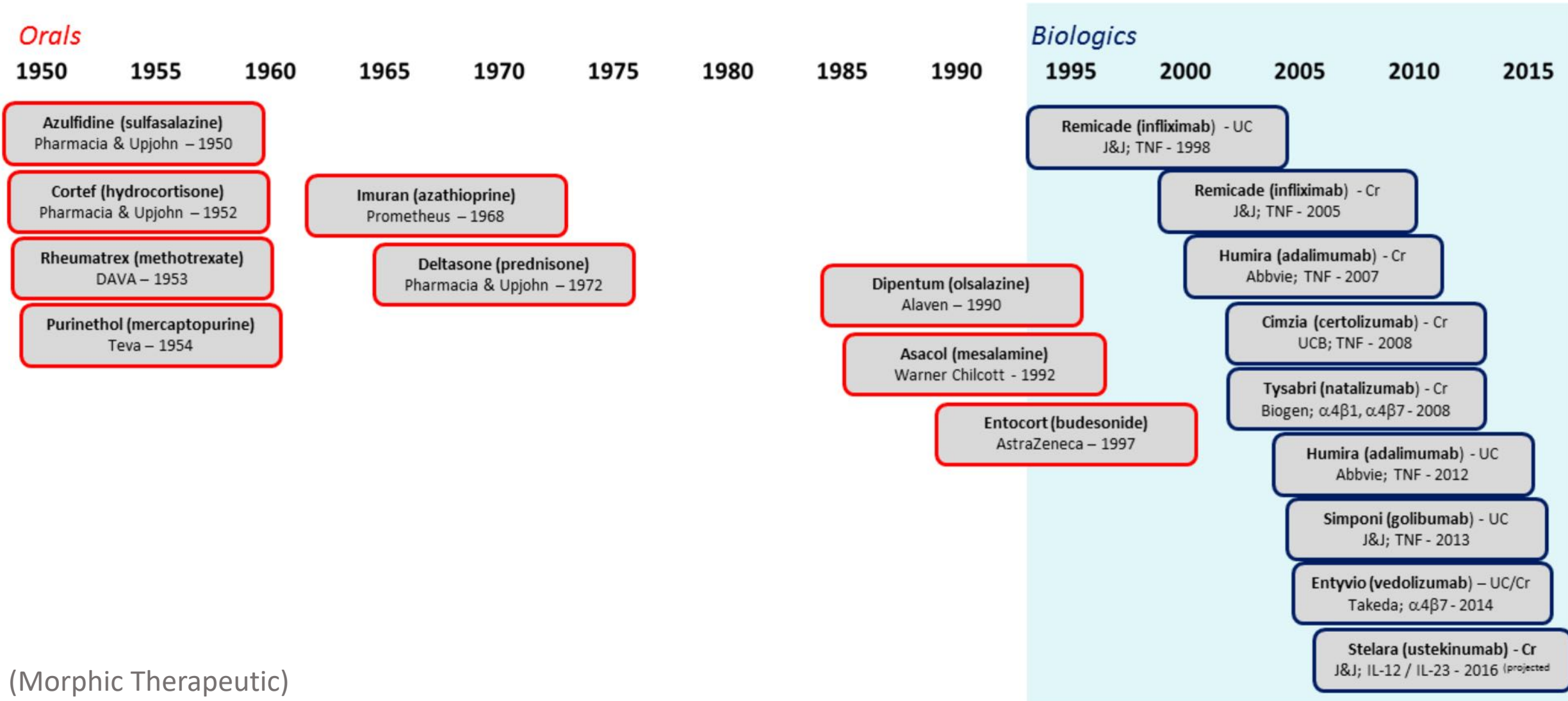


1st case of UC reported by Sir Walter Wilks

1st case of UC reported in China

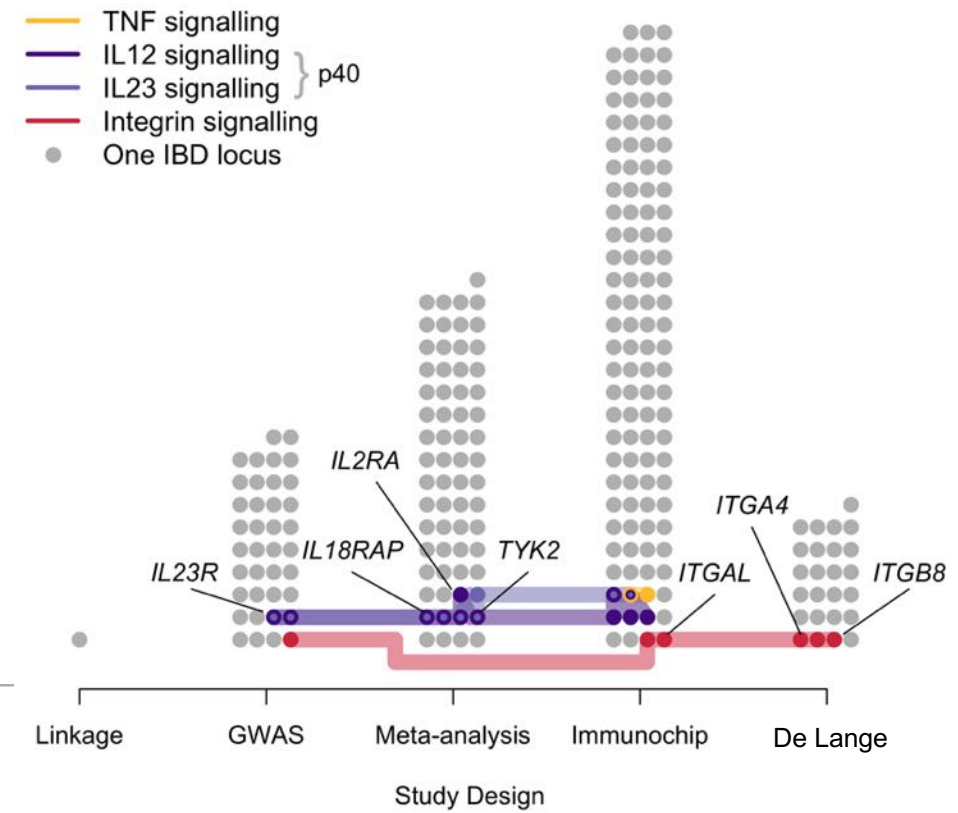
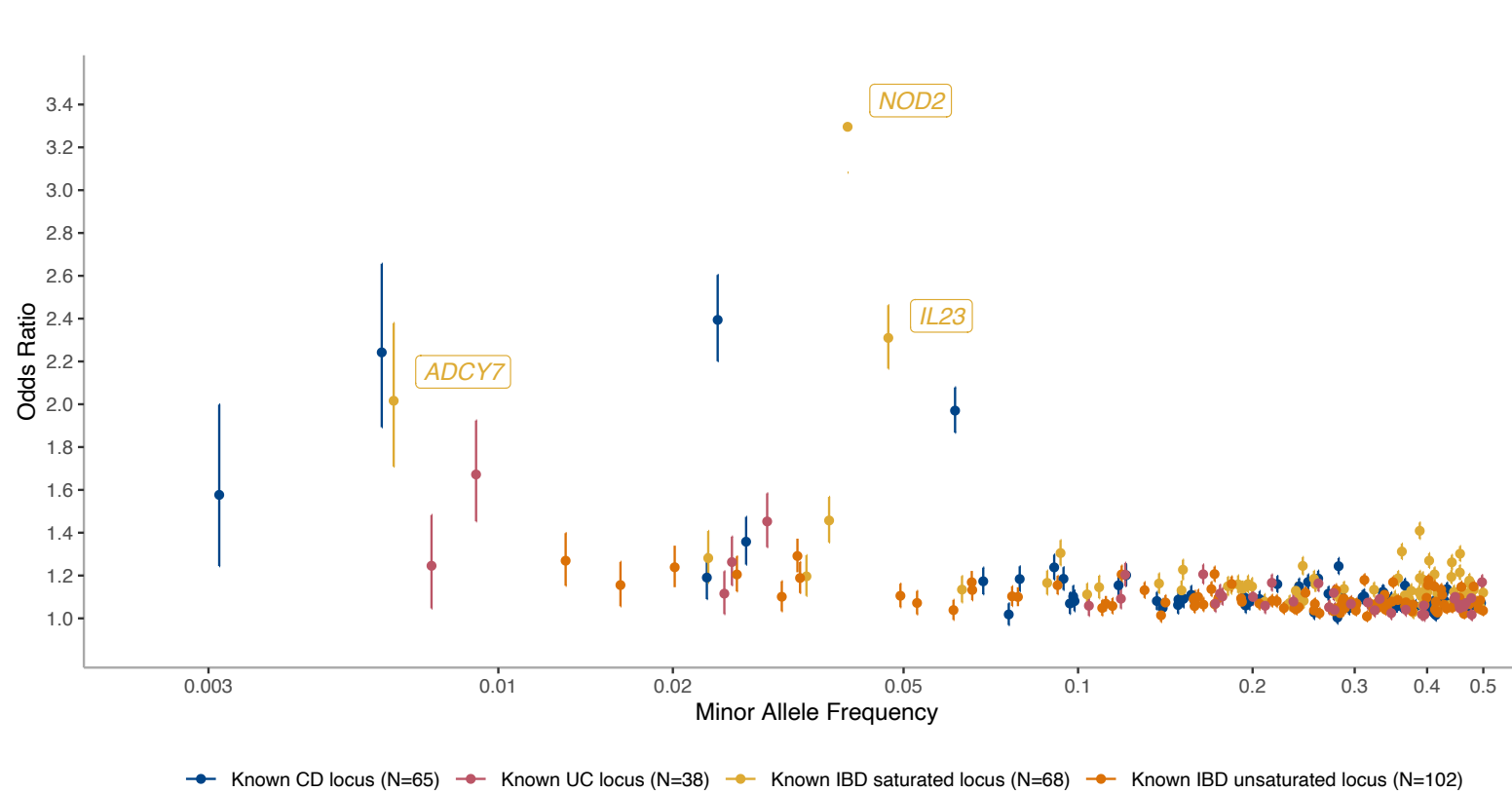


# IBD therapy development timeline



(Morphic Therapeutic)

# Genetics of IBD predisposition – many associated variants pointing to known drug targets



Left: Laura Fachal, right: De Lange et al. 2017





# Genome-wide association studies (GWAS)

Primary non-response (PNR) group



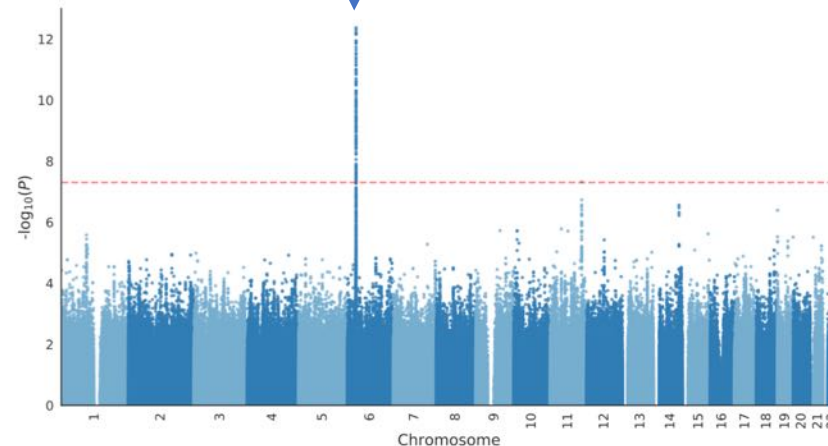
...ATCCAACA**G**TT...  
...ATCCAACA**G**TT...  
...ATCCAACA**C**TT...  
...ATCCAACA**G**TT...  
...ATCCAACA**C**TT...

Remission group



...ATCCAACA**C**TT...  
...ATCCAACA**C**TT...  
...ATCCAACA**G**TT...  
...ATCCAACA**C**TT...  
...ATCCAACA**C**TT...

≠  
Variant in different frequency in PNR group than in response group



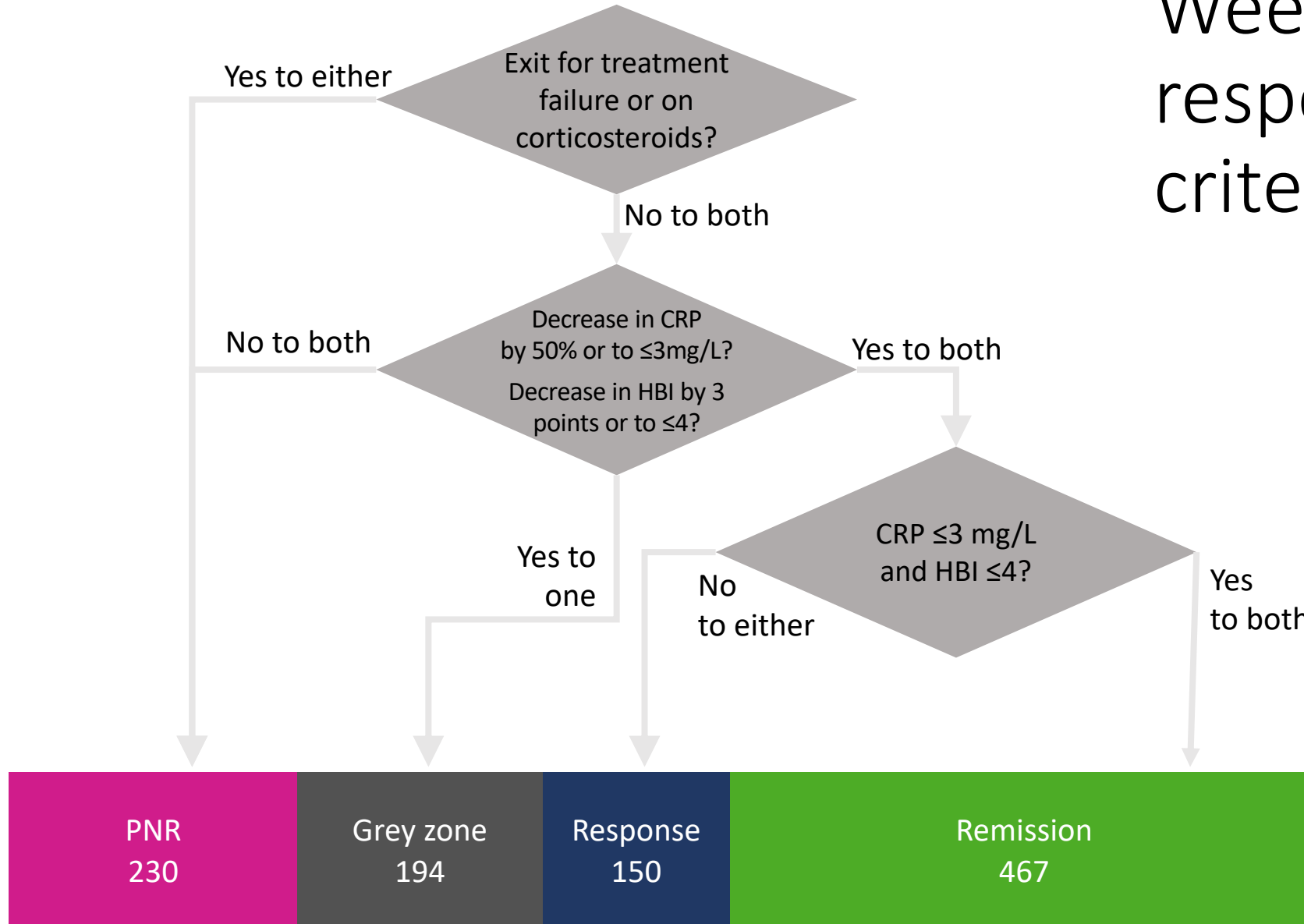
**Genotypes from DNA microarrays:**

1257 samples, after controlling for ancestry and relatedness

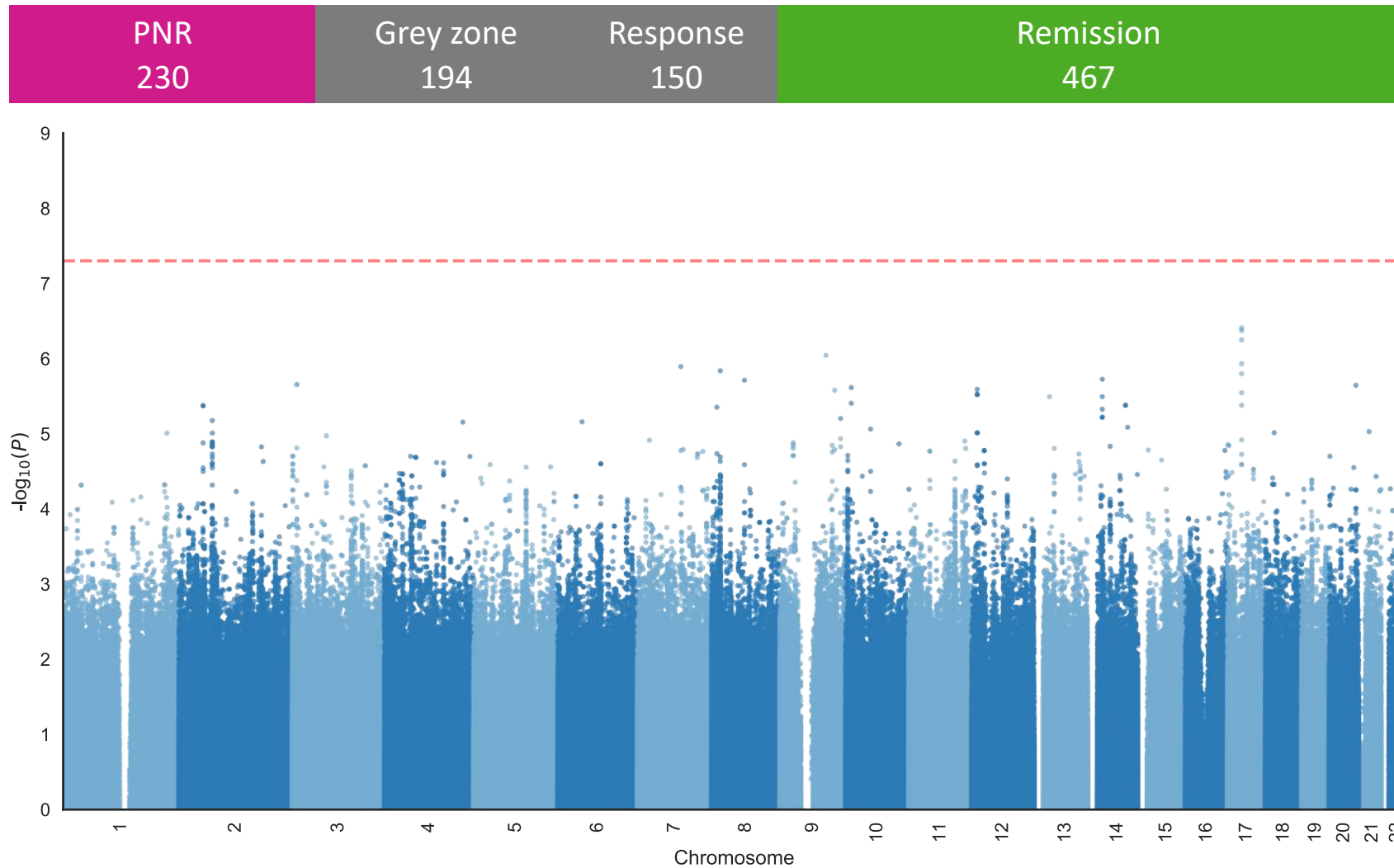
**Relevant covariates:**

sex, drug, immunomodulator status

# Week 14 response criteria

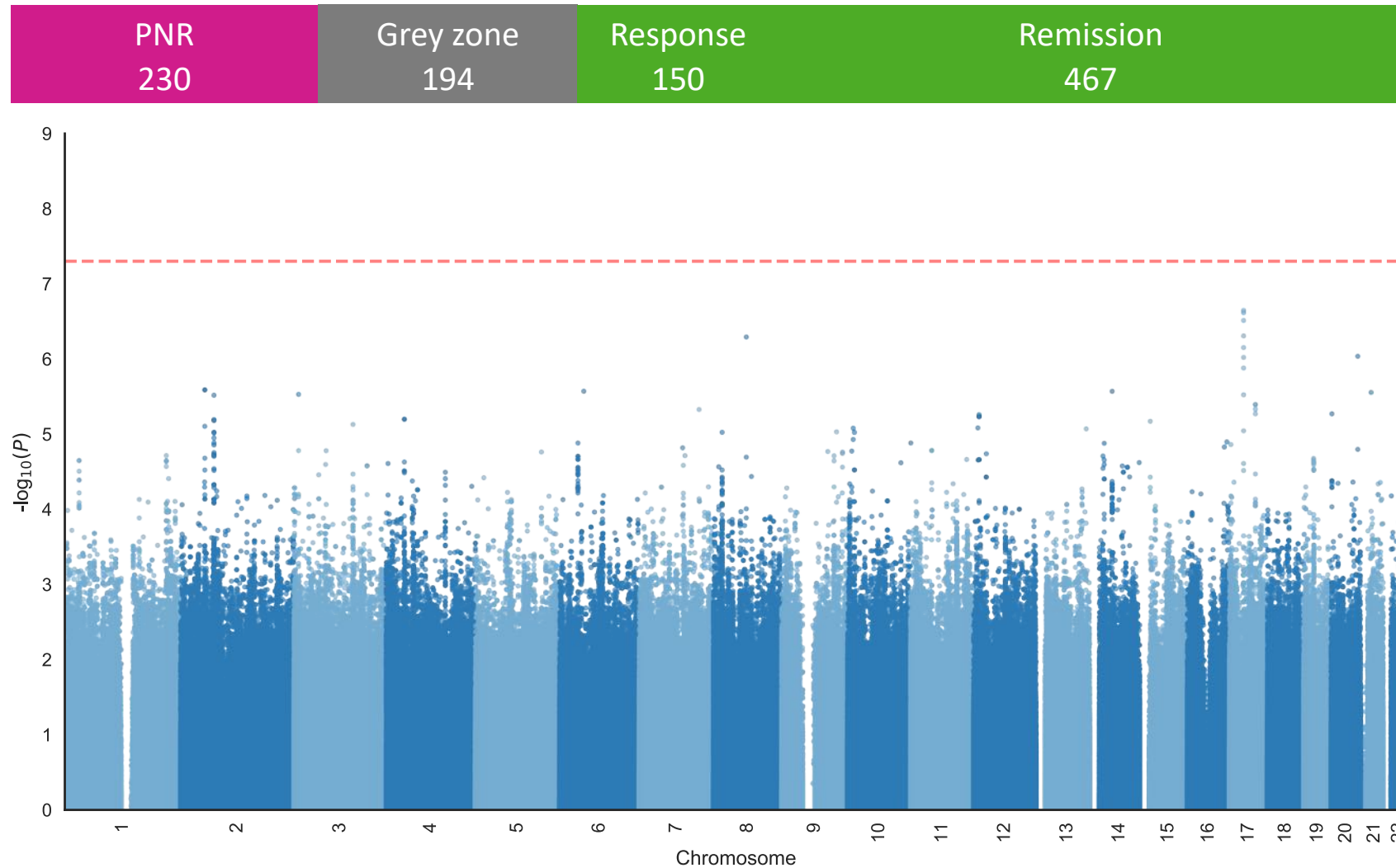


# PNR compared to remission

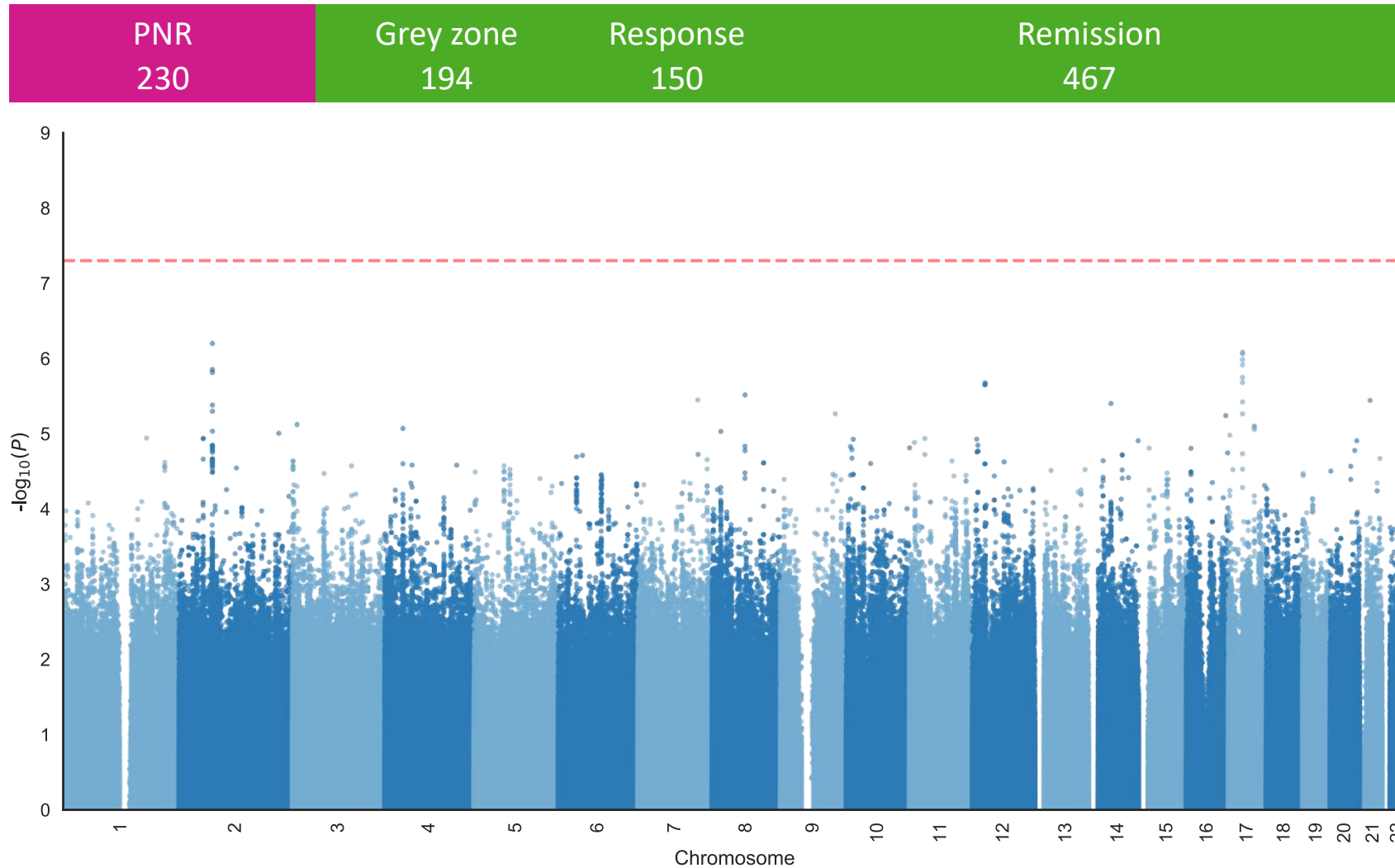




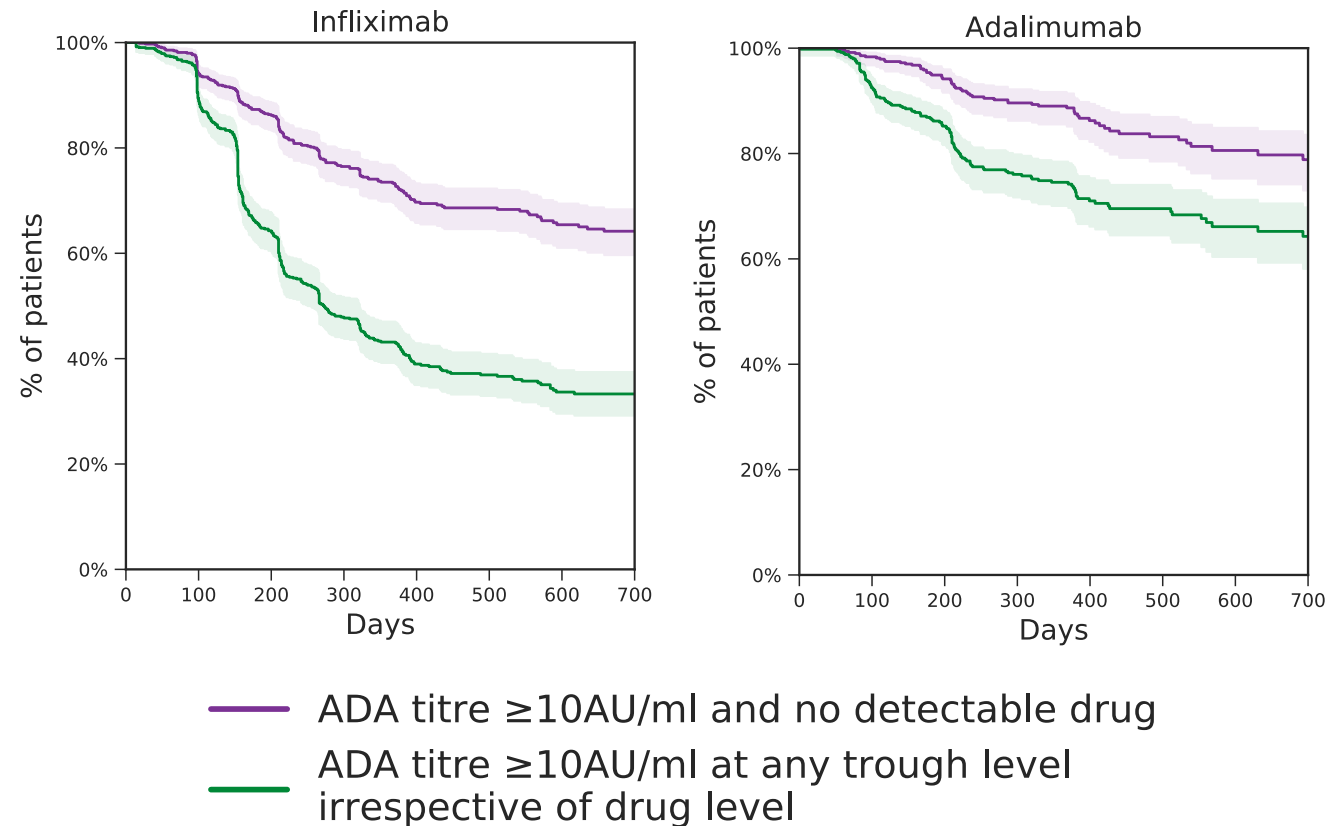
# PNR compared to response and remission



# PNR compared to grey zone, response and remission



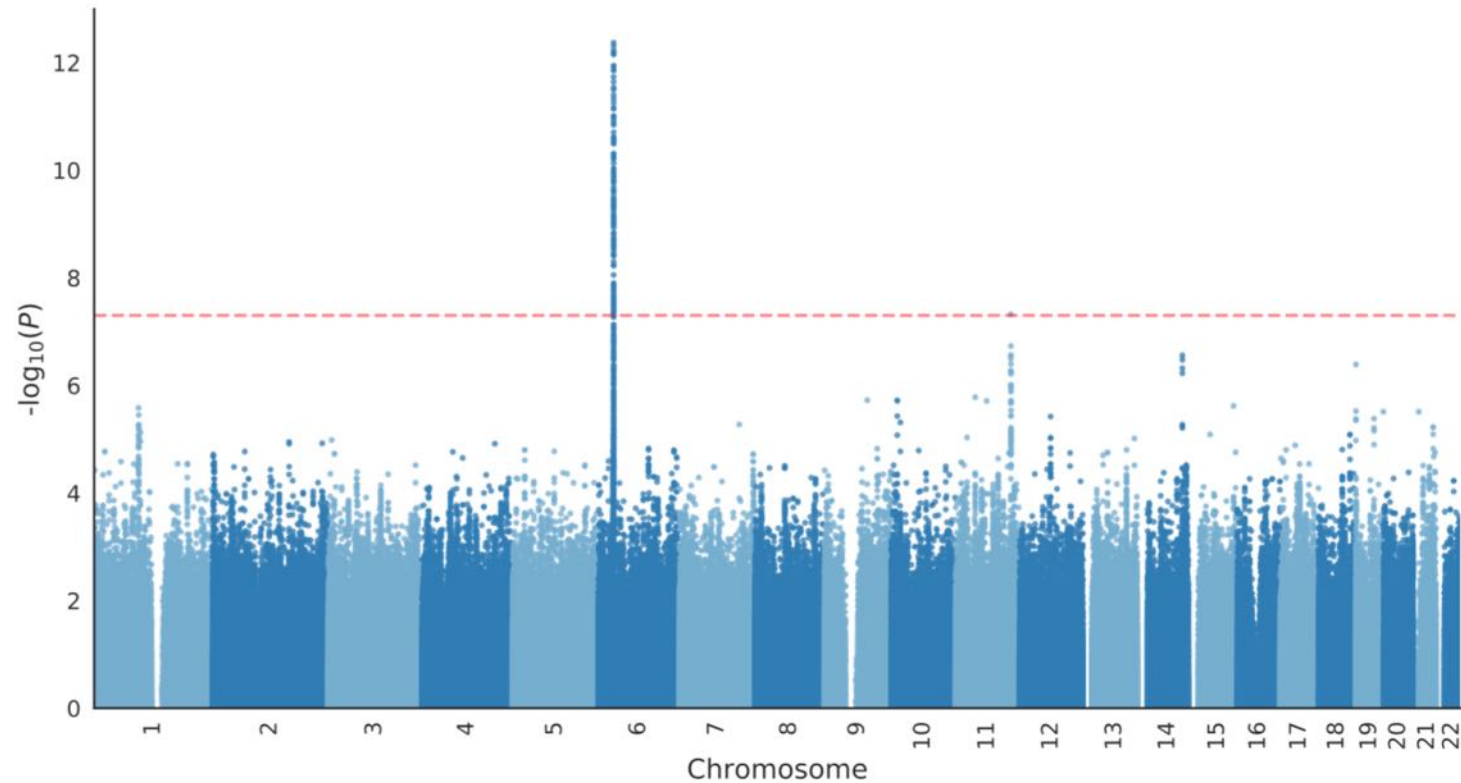
# Evolution of anti-drug antibodies *with or without detectable drug*



Anti-drug antibodies (ADAs) were measured serially at trough using the IDKmonitor **total** ADA b ELISA assay (see Nice et al., Aliment Pharmacol Ther. 2021 for validation)

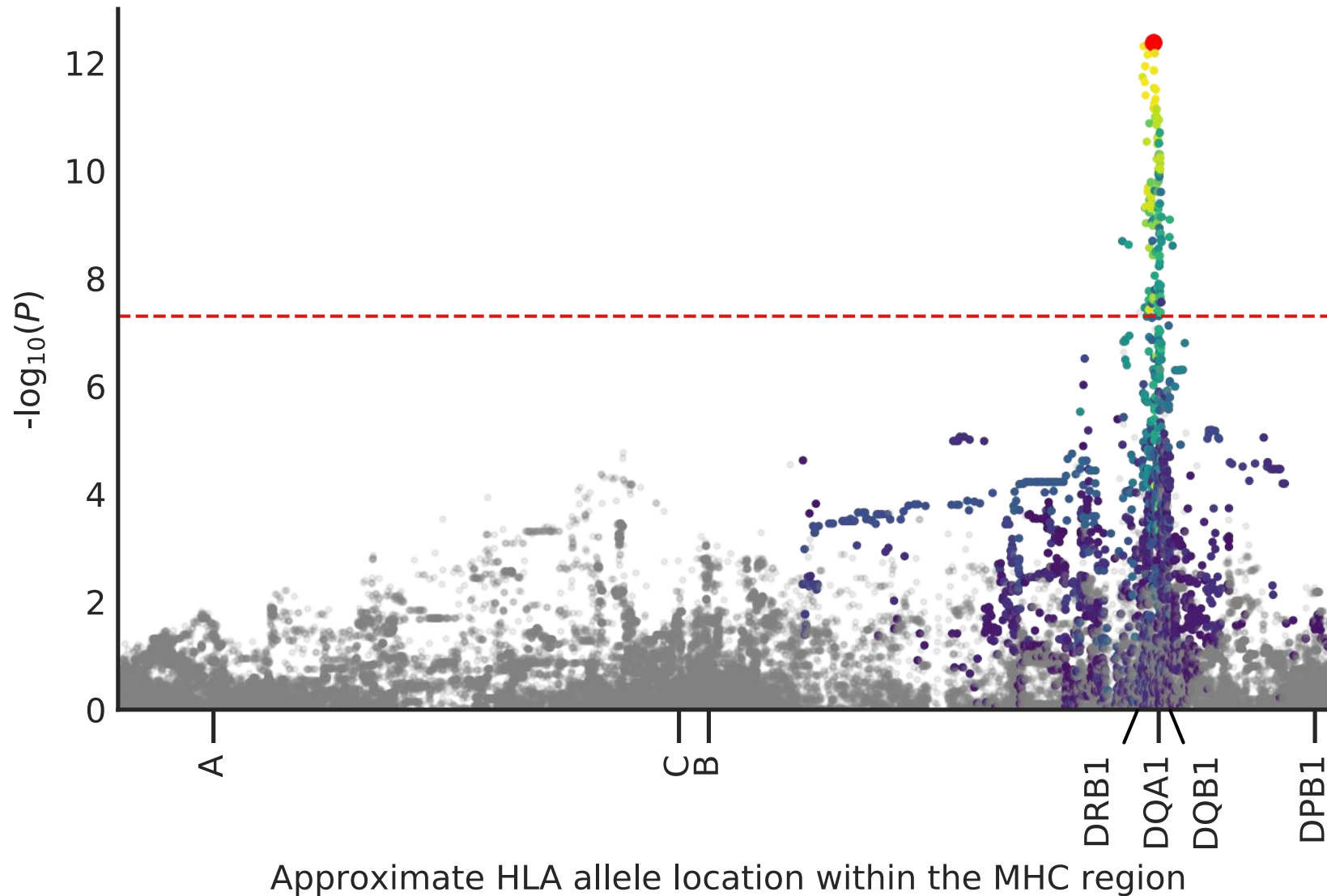
# Association to time of antibody development

*A strong signal on chromosome 6*

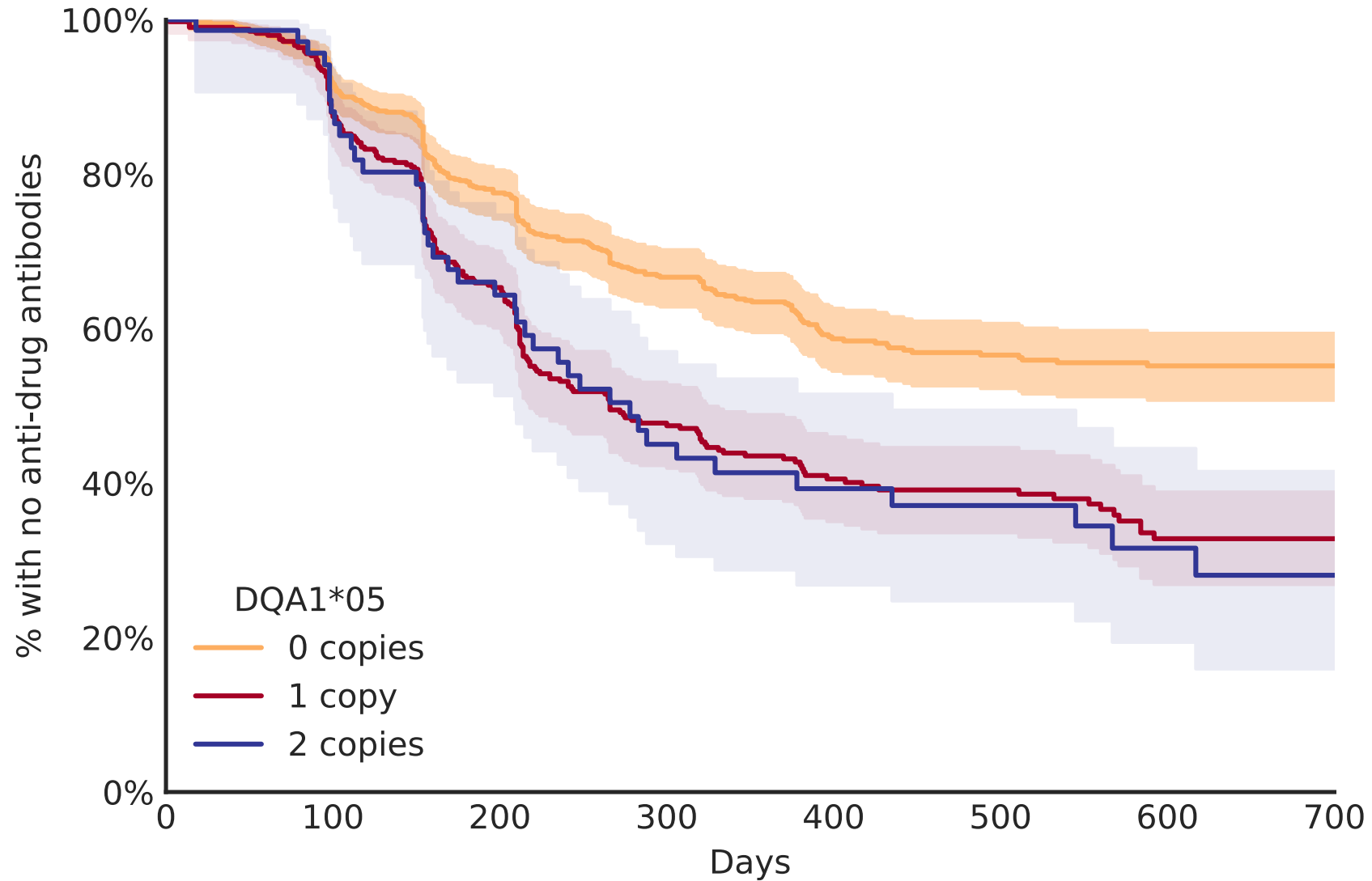


Chr.	Top variant	Minor Allele Frequency	Hazard ratio	P-value	Replication
6	rs2097432	20%	1.68	$4.2 \times 10^{-13}$	$7.84 \times 10^{-4}$
11	rs12721026	6%	0.46	$4.76 \times 10^{-8}$	0.49

# Understanding the signal on chromosome 6

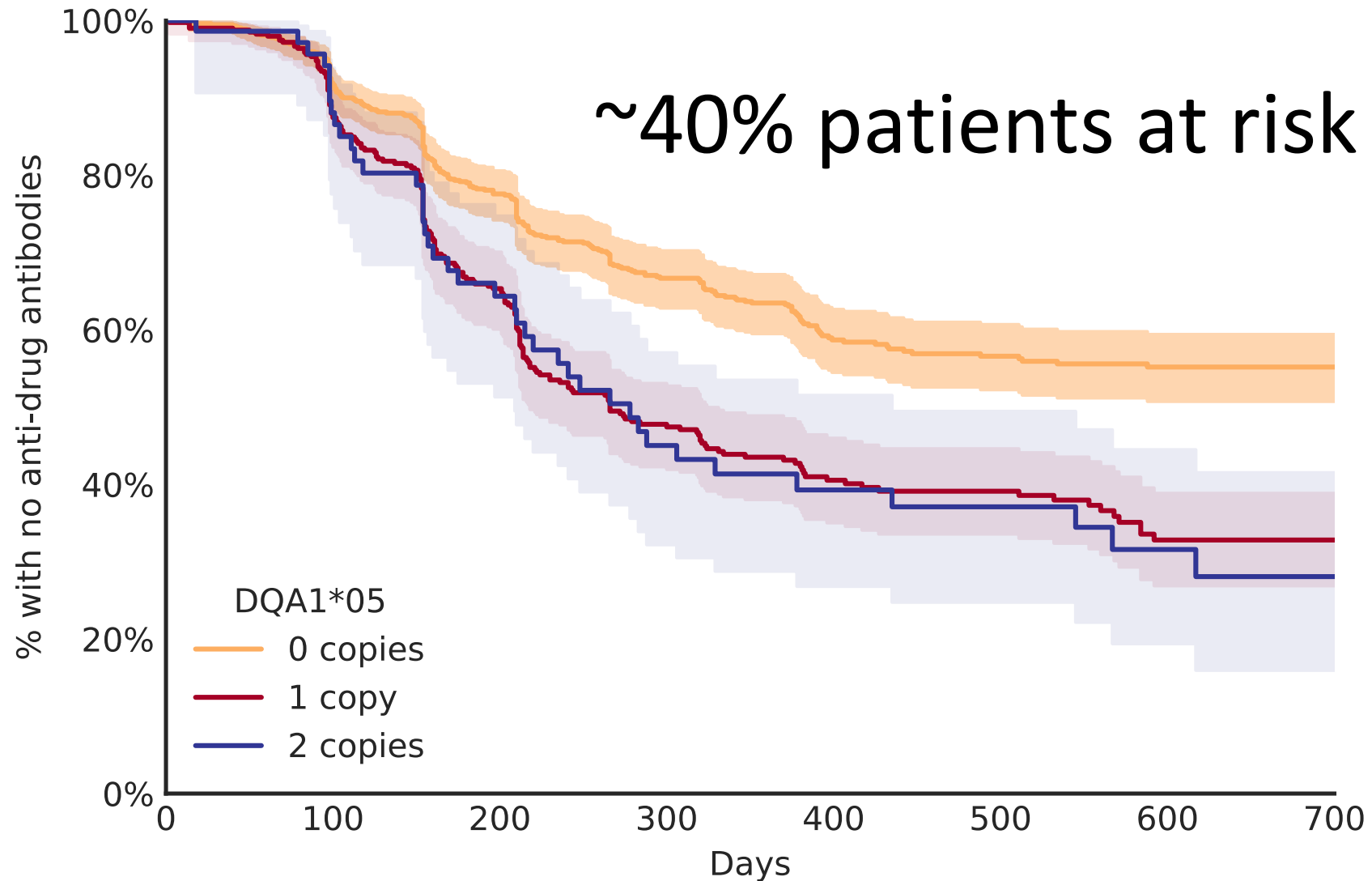


# HLA-DQA1\*05 underpins the association

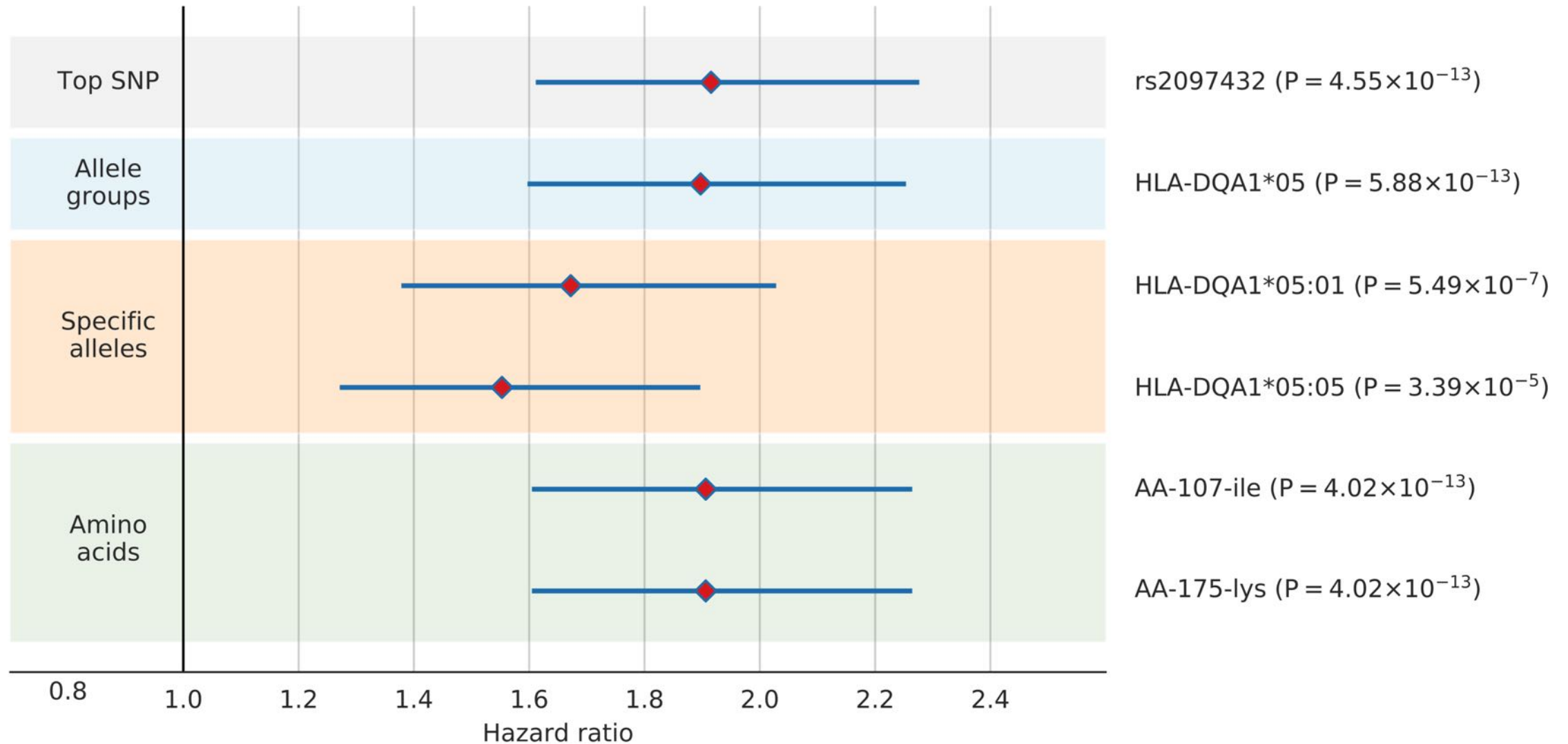




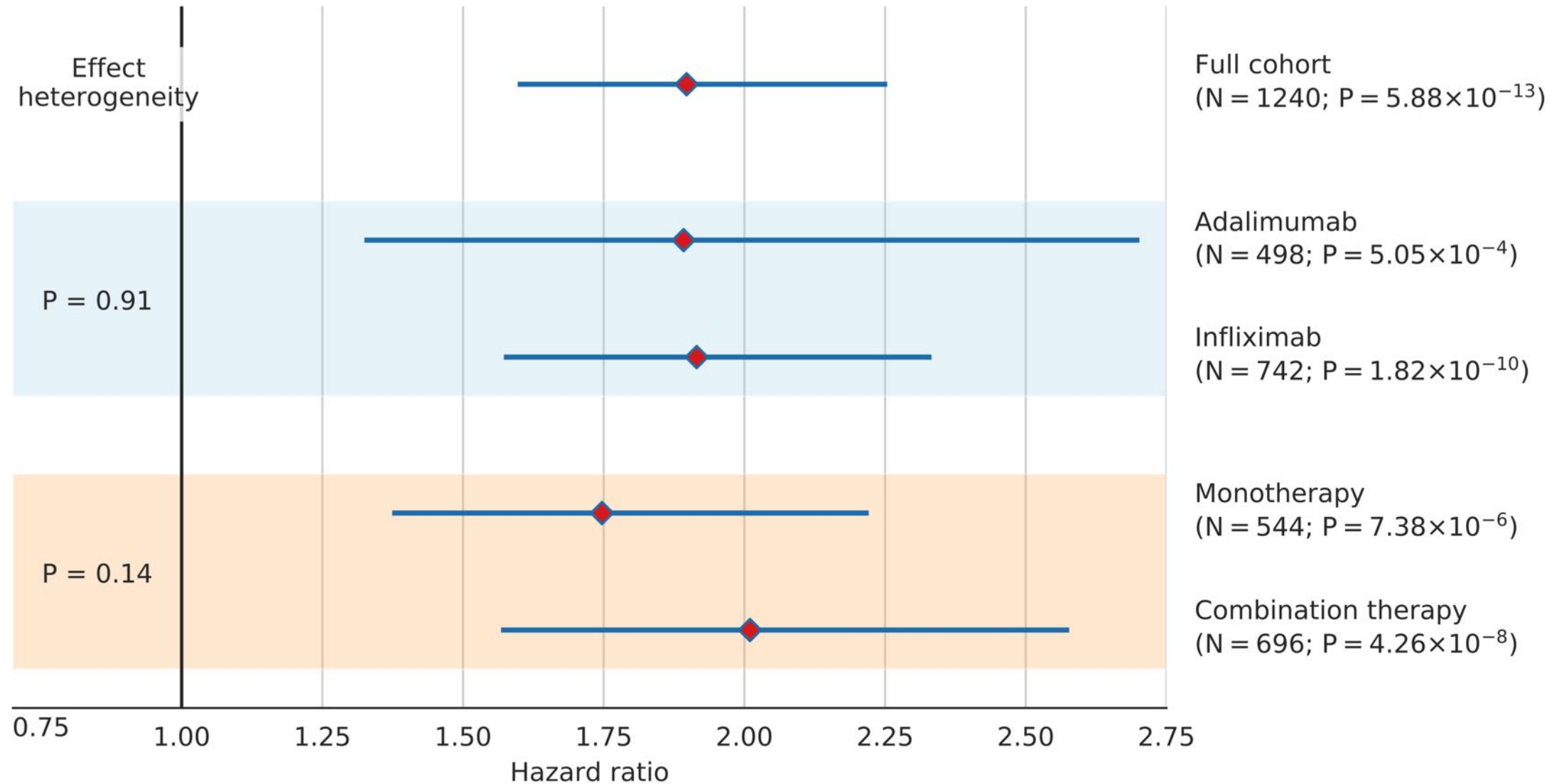
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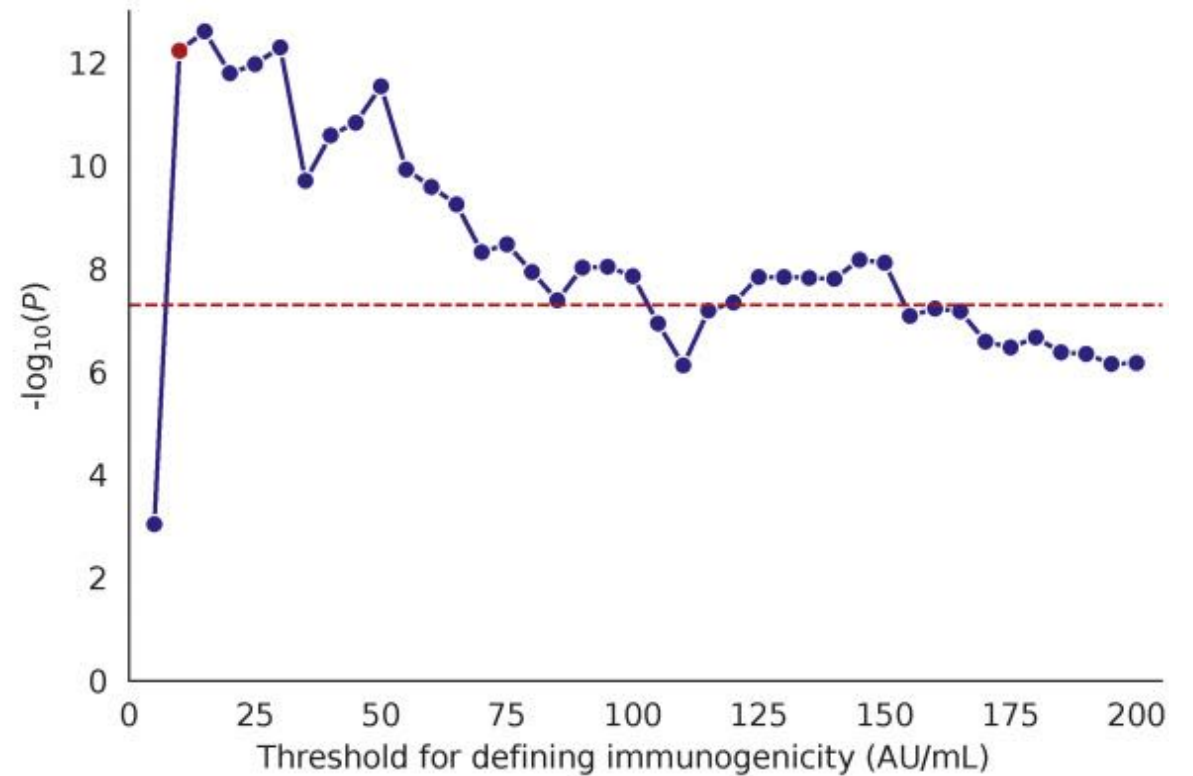
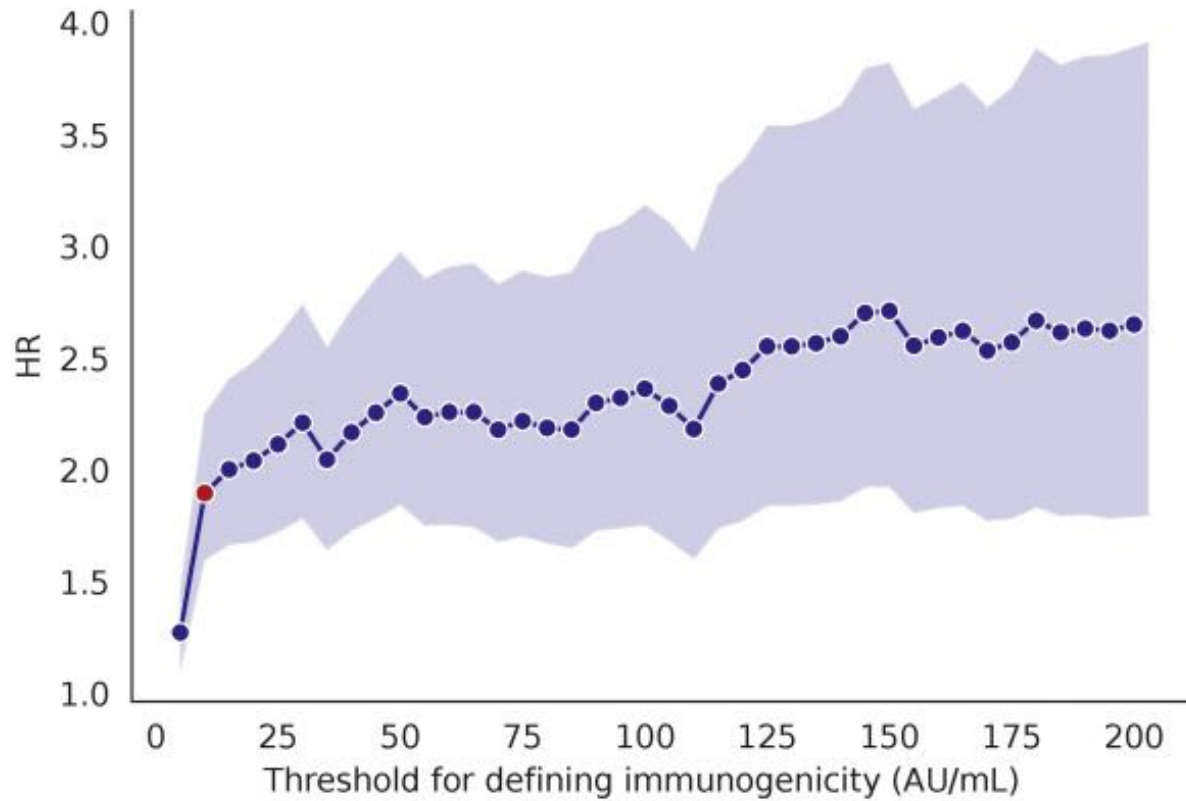
# HLA-DQA1\*05 underpins the association



# No evidence of effect heterogeneity

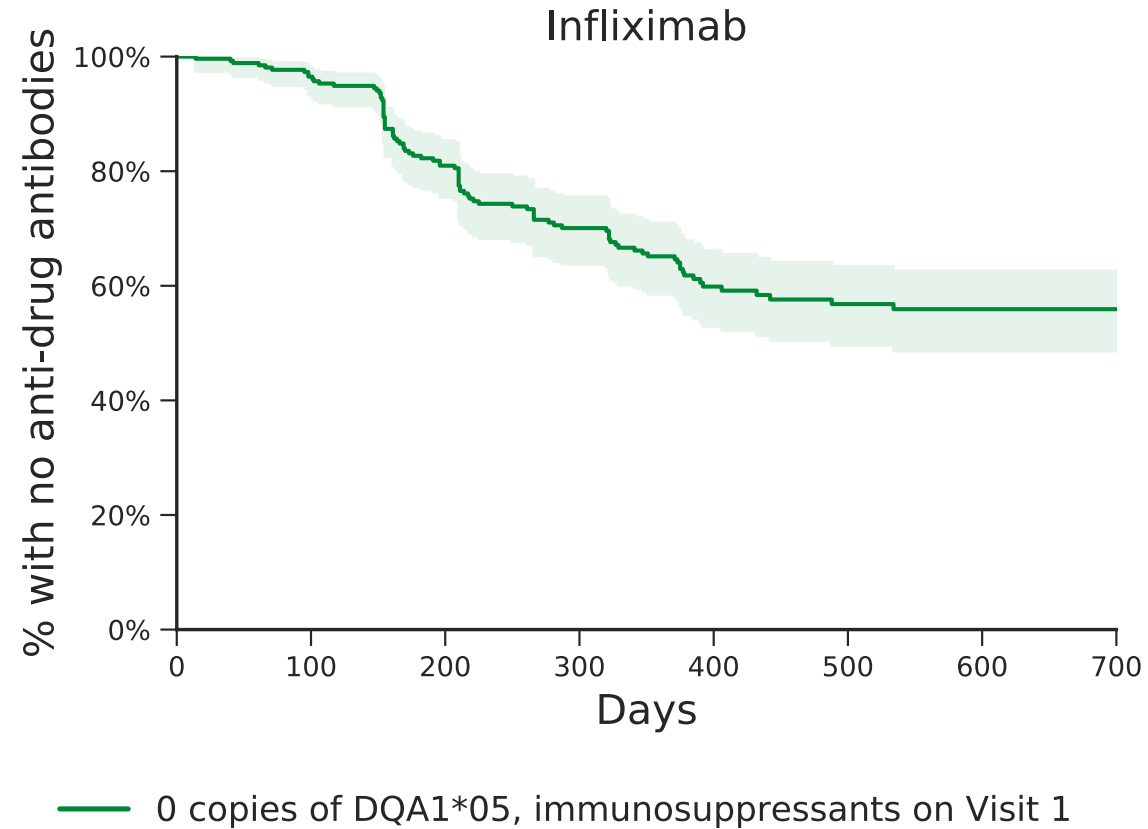


# Association holds up at higher immunogenicity thresholds

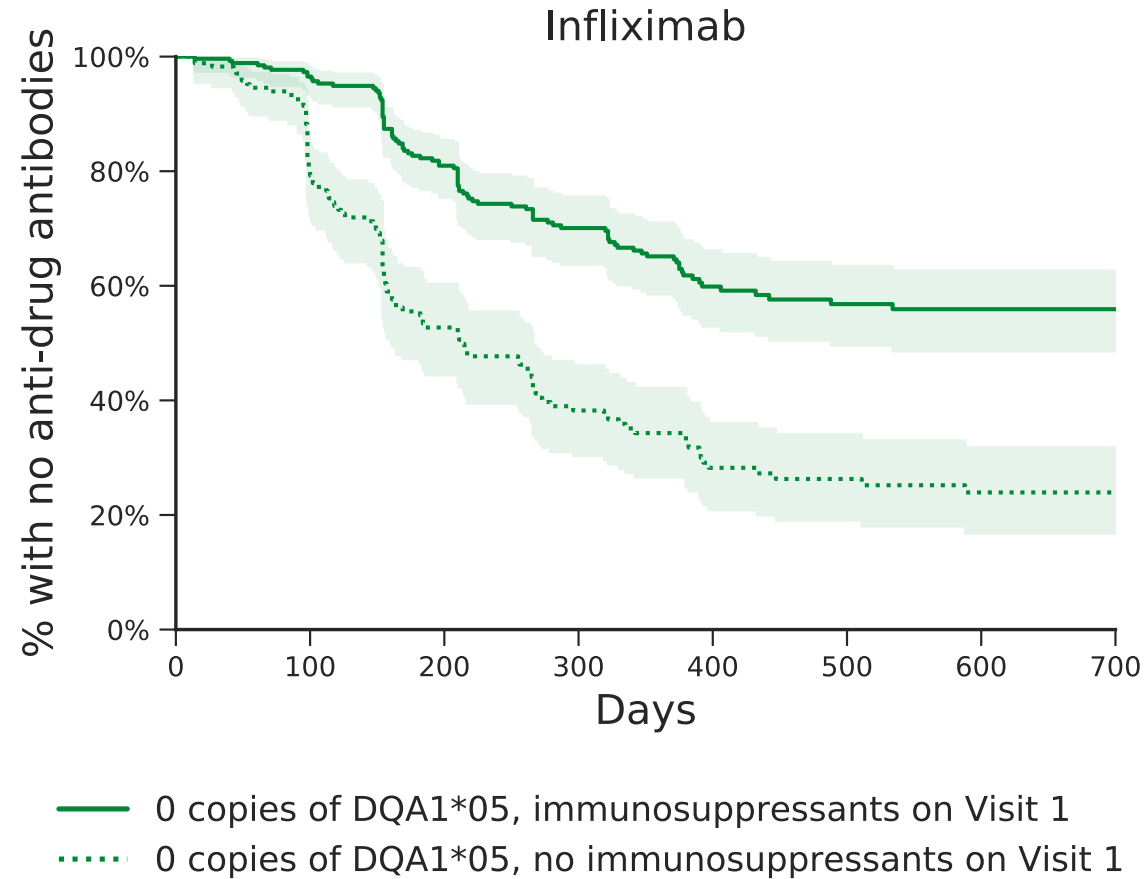


Additionally, carriage of HLA-DQA1\*05 was associated with higher maximal anti-drug antibody titers ( $P_{\text{infliximab}} = 8 \cdot 10^{-10}$ ;  $P_{\text{adalimumab}} = 0.002$ )

# Evolution of ADAs by genotype & immunomodulator (ADA titre $\geq 10$ AU/ml at any time)

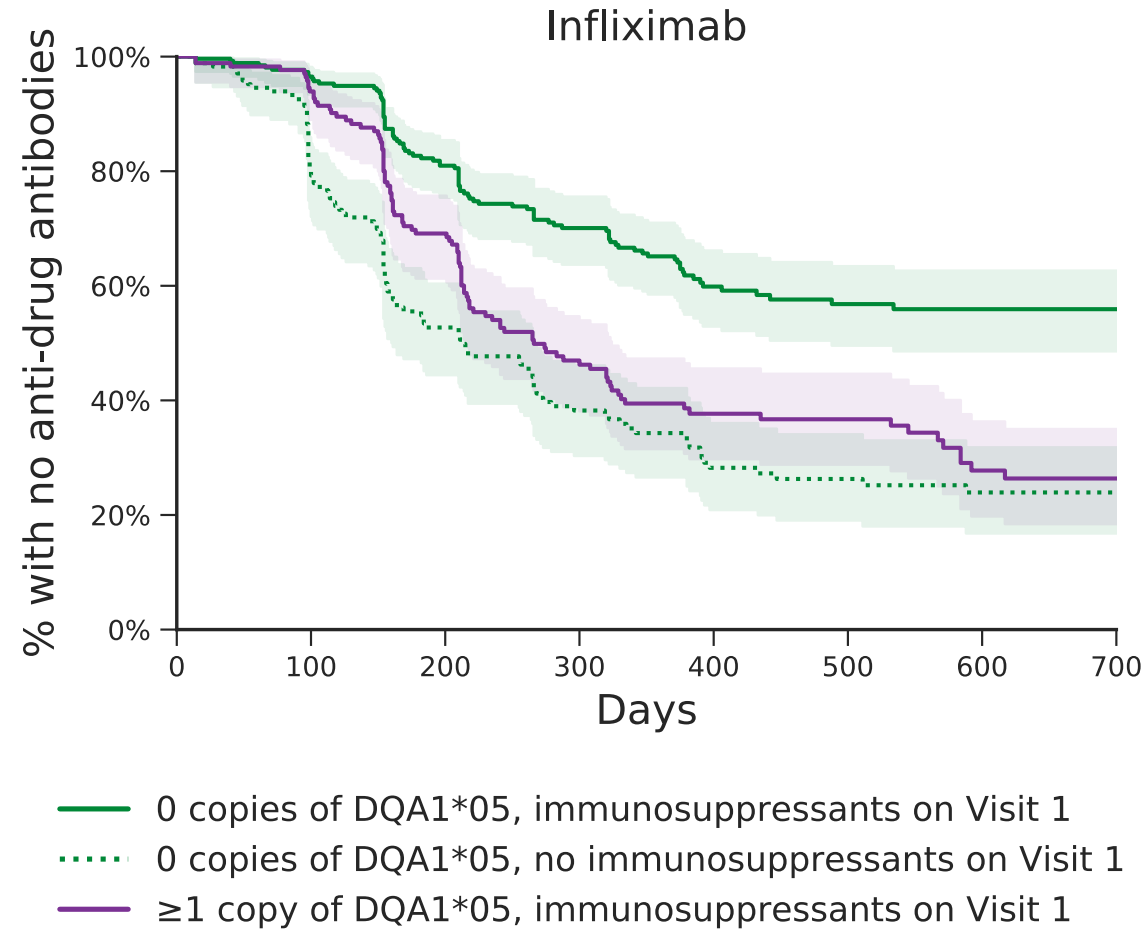


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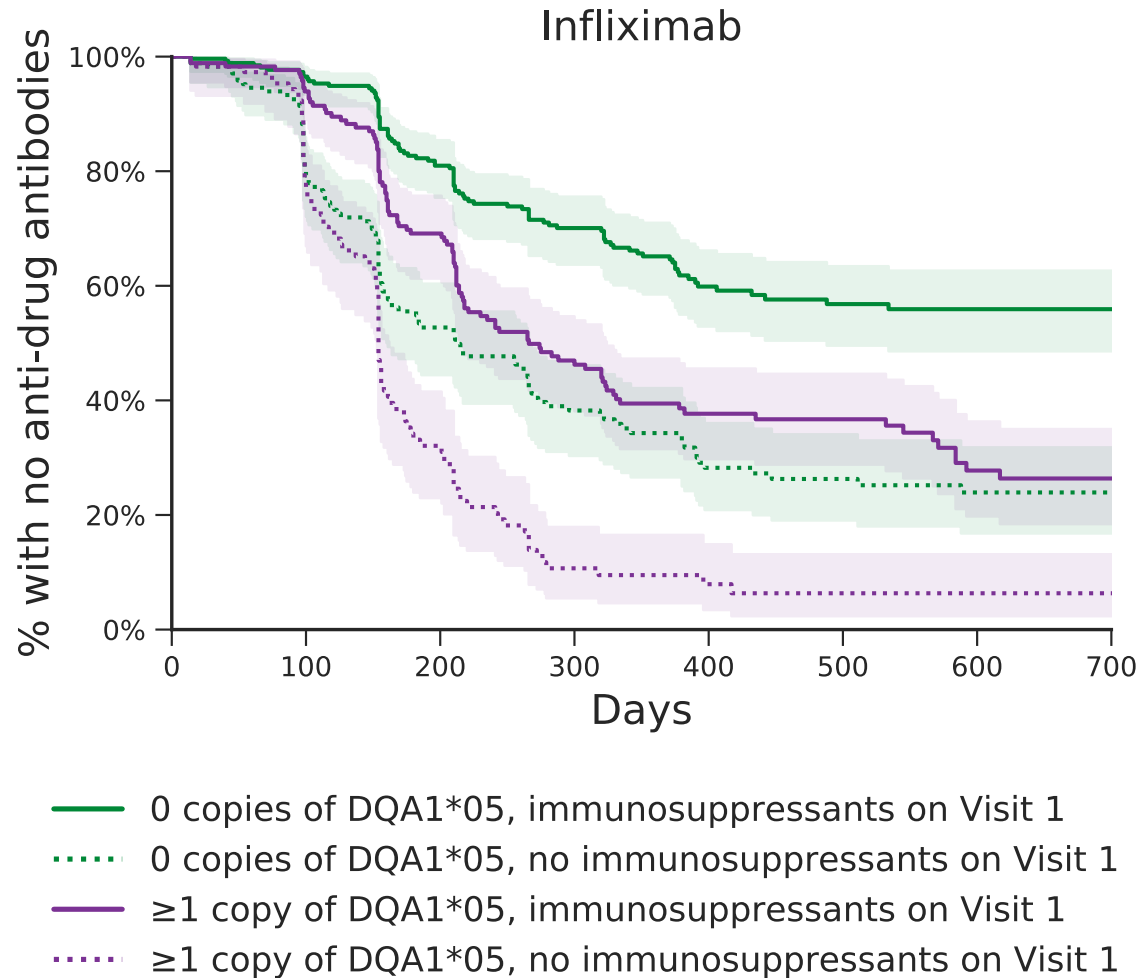




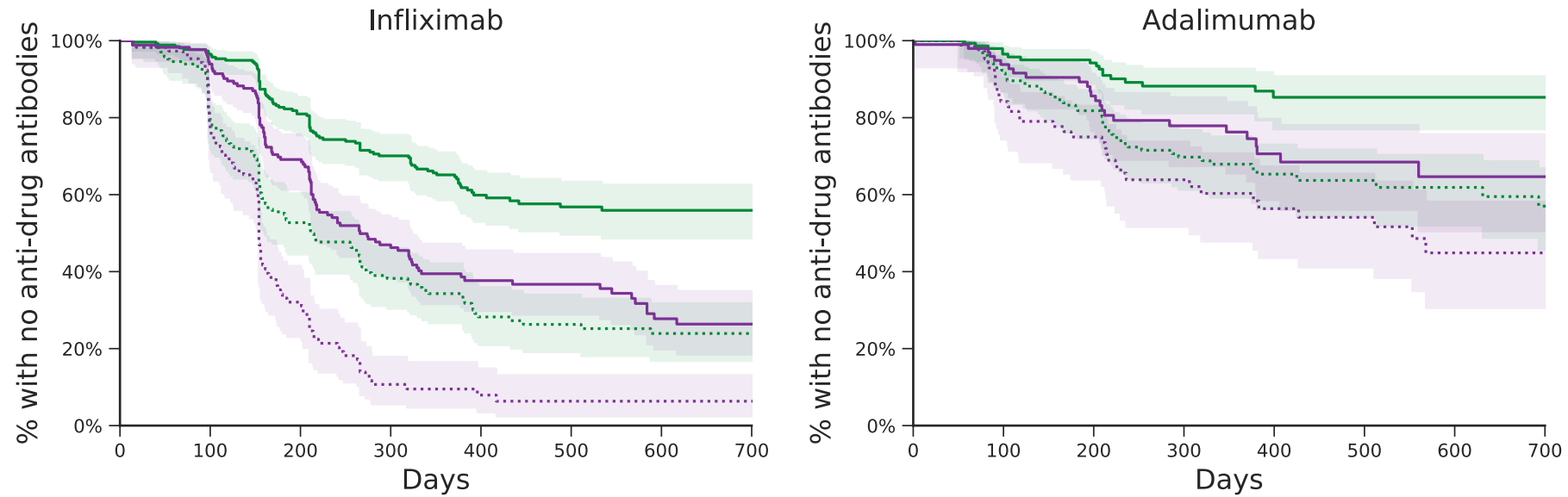
# Evolution of ADAs by genotype & immunomodulator (ADA titre $\geq 10$ AU/ml at any time)



# Evolution of ADAs by genotype & immunomodulator (ADA titre $\geq 10$ AU/ml at any time)



# Evolution of ADAs by genotype & immunomodulator (ADA titre $\geq 10$ AU/ml at any time)



- 0 copies of DQA1\*05, immunosuppressants on Visit 1
- ..... 0 copies of DQA1\*05, no immunosuppressants on Visit 1
- $\geq 1$  copy of DQA1\*05, immunosuppressants on Visit 1
- .....  $\geq 1$  copy of DQA1\*05, no immunosuppressants on Visit 1

# Potential clinical implications of DQA1\*05 association

The clinical implications of this association need to be explored before incorporating this marker into personalised treatment algorithms to maximise benefit and minimise harm from anti-TNF therapy

## **Questions:**

- 1. Should infliximab monotherapy be avoided in the ~40% of Crohn's patients who are DQA1\*05 +ve?**
- 2. Is this finding relevant to anti-TNF treatments in other diseases?**
- 3. Is this finding relevant to other biologics?**

# Next: Anti-TNF immunogenicity in IBD BioResource

- A cohort of 35,000 IBD patients, many on anti-TNF with linkage to health records and therapeutic drug monitoring for some
- Ongoing work on linking the drug monitoring data to research records
- 1115 patients with secondary loss of response and 3062 with sustained response (phenotyping work by Qian Zhang)

## Research questions:

- Further refining the HLA signal, searching for secondary associations
- Can we show: DQA1\*05 carriage → higher risk of loss of response?









# Acknowledgements

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Published manuscript: *Sazonovs et al., Gastroenterology, 2020*  
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# Disclosure of conflicts of interest

The PANTS study received grants from Abbvie, MSD, Celltrion, NAPP, Pfizer and Celgene, and non-financial support from Immundiagnostik, during the conduct of the study.

Aleksejs Sazonovs has no further conflicts of interest to report.

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## **Questions:**

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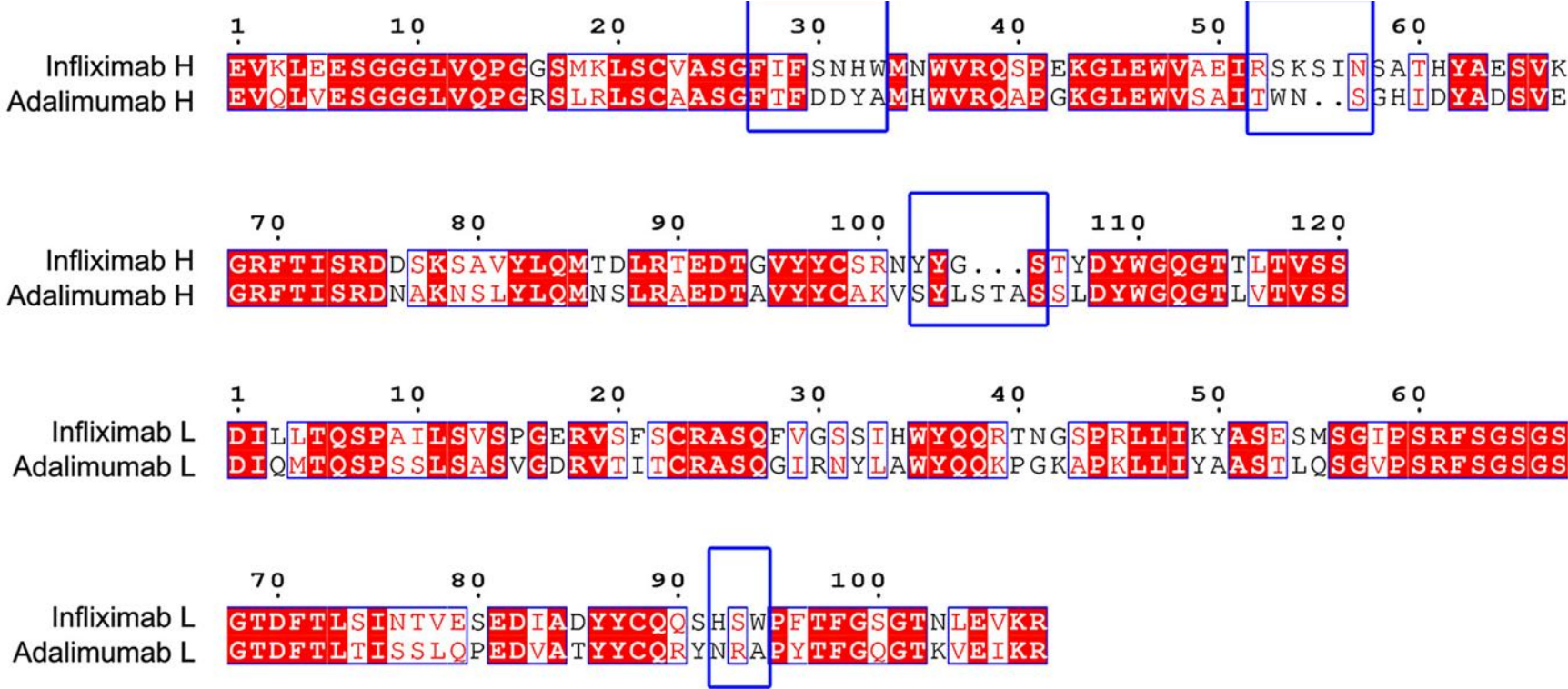
Higher risk immunogenicity rate to second anti-TNF in patients who developed antibodies against the first one

HMO-4 Immunogenicity to second anti-TNF therapy (IMSAT): implications for sequencing of biologic therapy **FREE**

Neil Chanchlani , Simeng Lin , Amanda Thomas , Ben Hamilton , Rachel Nice , Desmond Chee , Nick Kennedy , James Goodhand , Tariq Ahmad

**Results** Patients who developed immunogenicity to adalimumab (first) were more likely to develop immunogenicity to infliximab (second) (64% vs 40%,  $p < 0.001$ ), and patients who developed immunogenicity to infliximab (first) were more likely to develop immunogenicity to adalimumab (second) (34% vs 20%,  $p = 0.002$ ).

# Sequence comparison between infliximab and adalimumab

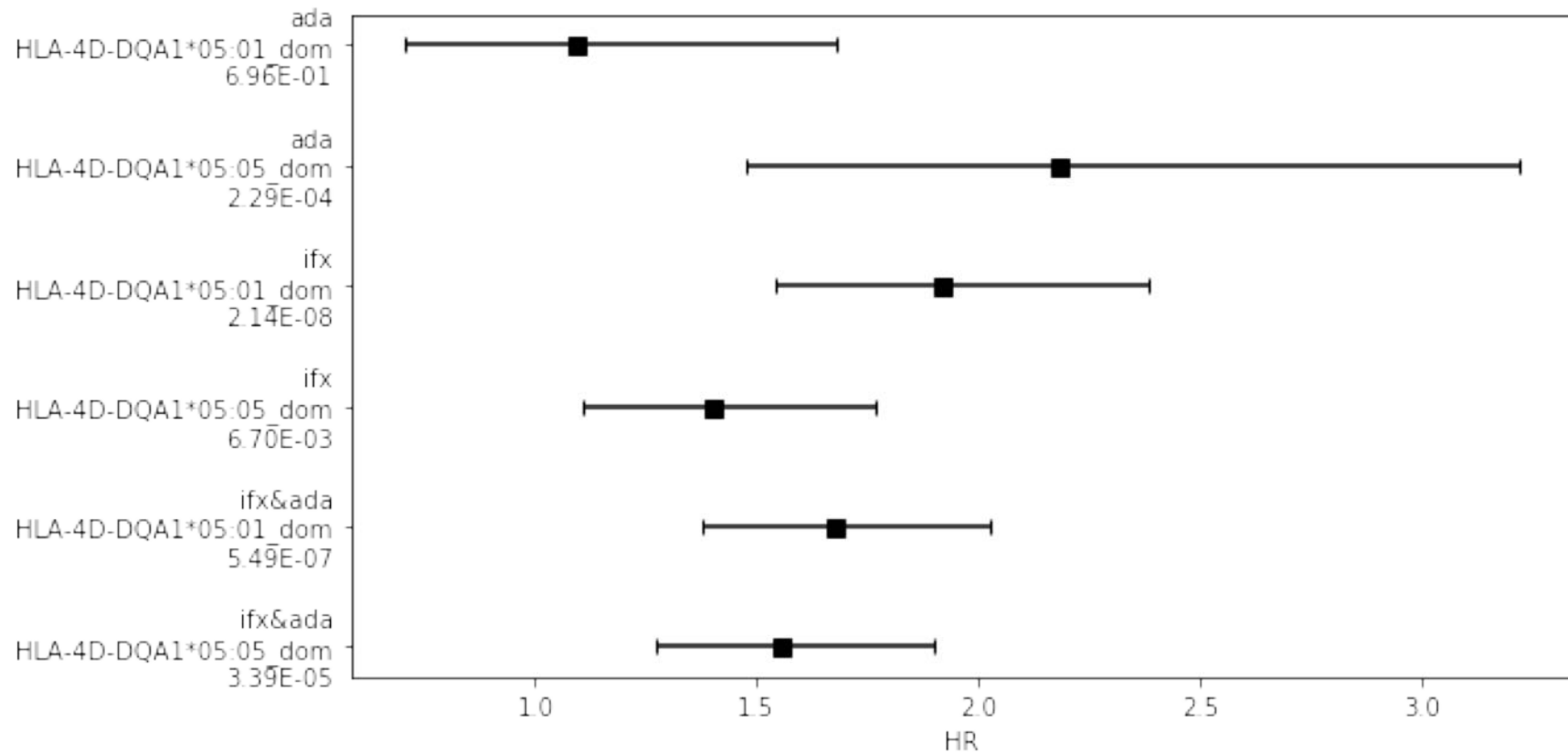


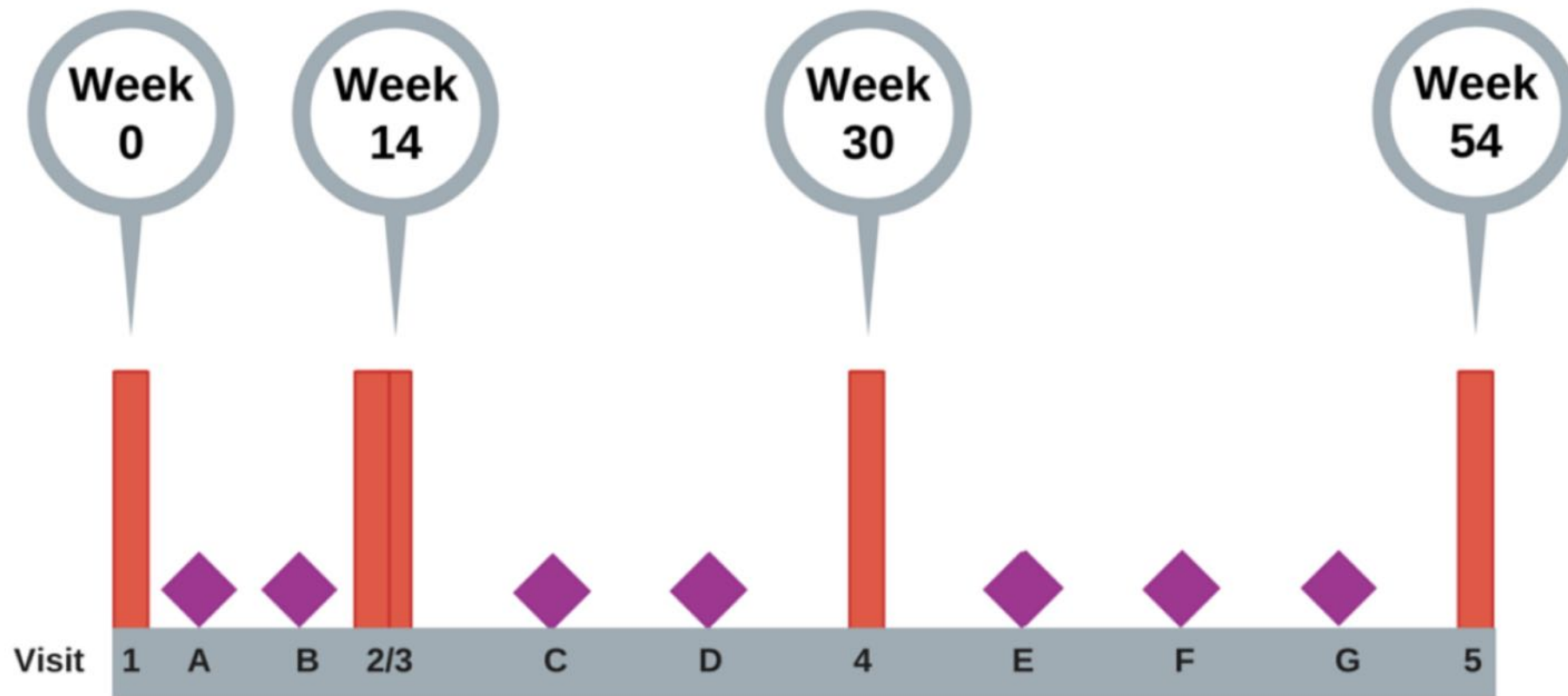
**“Sequence comparison between infliximab and adalimumab.**

The CDRs are highlighted by black frames and labelled. The residues that play crucial roles in the antibody-antigen interaction are framed with blue frames. Adopted from Hu S *et al*” from Liu *et al. PLoS One 2018*

Follow up is needed, please email me if you are interested!

# HLA 4D by drug





### Infiximab & Adalimumab

- CRP \*
- Drug and total anti-drug antibody levels \*
- Faecal Calprotectin \*
- HBI
- QOL - EQ5D, VAS, CCUQ-12/IMPACT III
- Serum for RNA \*
- DNA (Visits 1 and 5 only) \*
- BMI, Medications, Hospital Admission, Surgery, local lab tests, ADRs



### Infiximab Only

- CRP \*
- Drug and total anti-drug antibody levels \*
- HBI
- BMI, Medications, Hospital Admission, Surgery, local lab tests, ADRs

\* Assay performed at central lab



# Understanding the signal on chromosome 6

- The region includes the human leukocyte antigen (HLA) genes involved in immune response
- We have predicted the HLA alleles using statistical imputation techniques and have verified their accuracy
- Repeat the analysis at 2D and 4D resolutions and AA residues

